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(54) Title: INJECTABLE COMPOSITION

(57) Abstract: This invention relates to the stabilisation of ifosfamide solutions used in the treatment of tumours as parenteral infusion solutions. In particular, there is provided a liquid pharmaceutical composition for parenteral administration comprising ifosfamide, solvent and optionally, conventional pharmaceutical carriers and excipients, wherein said solvent comprises 35-75 % lower alcohol (based on the total weight of the solvent) and 25-65 % polyol (based on the total weight of the solvent). Said composition is preferably stable at refrigeration temperatures and higher for at least 30 days and more preferably at least 180 days. The polyol solvent is preferably propylene glycol, glycerol and/or polyethylene glycol of MW 200-600. The lower alcohol solvent is preferably ethanol.

INJECTABLE COMPOSITION

FIELD OF THE INVENTION

This invention relates to the stabilisation of pharmaceutical compositions used in the treatment of tumours, and particularly to the stabilisation of compositions delivered by injection.

BACKGROUND

The oxazaphosphorins are one of the group of alkylating cytostatic agents related to the nitrogen mustards which are widely used in the chemotherapeutic treatment of tumours. Oxazaphosphorins undergo electrophilic reactions with biological molecules including DNA whereby the alkylated DNA is damaged with respect to its replication mechanisms. Damaging the replication mechanisms ultimately effects cell viability leading to cell death. Oxazaphosphorins are effective regardless of the point in the cell cycle at which they are introduced. Rapidly proliferating tumour cells are especially sensitive to alkylating agents, and consequently cell death because the speed of their replication is not matched by DNA repair mechanisms.

The oxazaphosphorin of particular interest in relation to this invention is ifosfamide. Ifosfamide, a synthetic analogue of cyclophosphamide, has the chemical name (3-(2-chloroethyl)-2-[(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide) and is known to be effective against tumours, particularly germ cell tumours, sarcomas and lymphomas either as a single agent or in combination with other chemotherapeutic agents. Anti tumour activity by Ifosfamide (also known as Holoxan(R)) has been shown in ovarian, cervical, lung and breast cancer.

Therapeutic administration of oxazaphosphorins is typically via injection. Ifosfamide is indicated for intravenous use only usually over a period of at least several hours due to its toxicity. It is predominantly available in dry form and is supplied, for example, as a sterile, packaged dry powder for dissolution in water prior to administration, usually by infusion. Oxazaphosphorins including ifosfamide are however very subject to degradation by hydrolysis and accordingly prompt administration of such solutions is generally required. Ifosfamide is relatively stable by comparison to cyclophosphamide. However, prolonged storage of the dry

powder may result in sintering and yellowing, which in turn leads to a reduction in dissolution rate and a decline in pH. Reconstitution of powder-filled oxazaphosphorin products (such as ifosfamide) is characteristically slow. Even with vigorous shaking, 30 minutes or more may be required to ensure complete solution of the powder. Reconstitution times may be even longer if sintering or yellowing of the powder has taken place. Storage at elevated temperatures also leads to degradation, as does the use of temperature to speed the dissolution process. Although not directly related to degradation, any degree of discolouration is considered indicative of degradation and accordingly discoloured solutions of oxazaphosphorins are generally discarded.

To overcome difficulties associated with the thermal and hydrolytic susceptibility, lyophilization of the drug has been tried. This process involves freeze drying, whereby ice is sublimed from frozen solutions leaving only the solid, dried components of the original liquid.

Lyophilization has several advantages over the previous dry powder formulations. Lyophilization permits pharmaceuticals which are unstable in aqueous solution, yet relatively stable in the solid state to be processed and filled into dosage containers in solution, taking advantage of the relative ease of processing a liquid, dried without elevated temperatures, thereby eliminating adverse thermal effects and then stored in the dry state in which there are relatively few stability problems.

However, there are disadvantages associated with this process. Lyophilization requires sophisticated vacuum pumps, sterile, refrigerated chambers with meticulous thermal controls for cooling samples, condensers to trap the water vapor as it sublimes from the frozen solution, and thermocouple probes for monitoring product temperature. The apparatus itself, the energy and the technicians required to run it become quite expensive on an industrial scale and raise the cost of the product accordingly.

Lyophilization is also inefficient. Lyophilization involves removing water from a frozen aqueous solution leaving a freeze-dried solid. The freeze dried solid is delivered to the customer, who, when necessary, reconstitutes the drug as an aqueous solution. Clearly, if the lyophilization process could be circumvented, time and cost would be reduced.

Finally, the lyophilized or dry powder product must be reconstituted. Reconstitution necessitates some degree of personnel exposure. This is particularly undesirable when the drug is a strongly cytotoxic antineoplastic agent such as the oxazaphosphorins including ifosfamide. This hazardous exposure is aggravated by aerosolization of the cytotoxic agent that might occur during reconstitution. As a lyophilizate the drug must be dissolved prior to injection. This necessitates additional entry to the vial with a syringe to add the solubilizing liquid vehicle. With each accession of the vial small quantities of the drug become airborne and this is known as aerosolization. Such added exposure requires particular precautions such as rubber gloves and masks. Furthermore, reconstitution introduces potential for dilution errors. This reconstitution can take up to 30 minutes, which is very inconvenient and time consuming. For these and other reasons producers and consumers alike prefer readily injectable liquid formulations of parenterally administered drugs.

Attempts have been made to provide a product which can be supplied in solution in a ready-to-dilute form but which is stable for a sustained period in the undiluted form. Such a product would be advantageous at least because of the ability of the user to omit the step(s) of dissolving or reconstituting a solid product prior to administration. However, the preparation of directly injectable stable aqueous or water containing oxazaphosphorin solutions is not possible due to the instability of these compounds as mentioned hereinabove.

US 4952575 (ASTA PHARMA AKTIENGESELLSCHAFT) discloses solutions containing an oxazaphosphorin in which the active agent is dissolved in very high concentrations (up to 100%) of ethanol. Two examples are provided; one providing a 25% cyclophosphamide solution containing 96% ethanol and the other providing a 25% ifosfamide solution also containing 96% ethanol. Ifosfamide is shown to have an annual decomposition rate of 0.3% at 20°C and cyclophosphamide is shown to have an annual degradation rate of 15% at 20°C when formulated according to this disclosure in 96% ethanol. Whilst high concentrations of ethanol reduce the degradation of the oxazaphosphorin by hydrolysis, they lead to other problems arising from the volatility and flammability of the ethanol. Theoretically the formulation of this patent should avail the user of a product stable at room

temperature. However, the volatility of ethanol at these temperatures leads to significant handling problems. In particular, higher volatility due to the use of pure ethanolic formulations may lead to greater difficulty in manufacturing and filling the product since weight loss, flammability and solvent extraction issues will be greater. Furthermore, owing to the low viscosity and low surface tension of ethanol, too high a quantity of ethanol as solvent will lead to syringing difficulties; particularly, the solution may run out of the syringe during delivery.

US 4879286 (Lyphomed, Inc.) discloses ready-to-dilute solutions of cyclophosphamide which are formulated by dissolving the active agent in an organic solvent such as a polyol. It is suggested that a desirably stable product can be achieved by a solvent of 50 – 100% organic polyol and 0 – 50% water. The water may be in part replaced by 10 – 30% ethanol based on the total weight of the formulation. The examples suggest that these solutions are stable at 4°C (refrigerator temperature) for several weeks but show insufficient stability at room temperature or higher.

WO 99/18973 (STADA) discloses ifosfamide in a sodium chloride solution. The patent claims stability at refrigerated temperatures but tests show that at elevated temperatures (50°C), the product is unstable over any period longer than 4 weeks. This is corroborated by the document itself.

It is one aim of this invention to provide an ifosfamide solution in a ready-to-dilute form, which is stable at conventional handling temperatures over a sustained period. It is another aim of the invention to provide improved methods of delivering parenteral oncological medical treatments using ifosfamide.

SUMMARY OF THE INVENTION

Thus, in a first aspect of the invention there is provided a liquid pharmaceutical composition for parenteral administration comprising ifosfamide, solvent and optionally, conventional pharmaceutical carriers and excipients, wherein said solvent comprises 35–75% lower alcohol (based on the total weight of the solvent) and 25–65% polyol (based on the total weight of the solvent).

It is surprisingly found that the compositions according to the invention are chemically stable to hydrolysis, may be produced in low volume and with only a small quantity of excipients with the resultant logistical benefit of being easily

packaged and transported, and the clinical benefit of both time and convenience including the fact that the need to reconstitute the product can be substantially avoided. In addition the composition of the invention has been found to have a viscosity ideally suited to delivery by syringe thereby allowing ease of handling. In particular, the viscosity is sufficiently low as to allow easy handling with a syringe, but also sufficiently high as to reduce the likelihood of seepage of the product from a syringe. Loss of solvent through excessive evaporation is also substantially avoided.

Throughout this specification, the terms "comprises/comprising" should be taken to specify the presence of stated features, integers, steps or components but does not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

Furthermore, the term "liquid" when used throughout this specification should be taken to mean that the compositions of the invention are in a fluid state.

The term "stable" when used throughout this specification should be taken to mean that the liquid pharmaceutical compositions according to the invention are, in their state at a specified stage post manufacture, acceptable for pharmaceutical usage in a patient.

The term "lower alcohol" when used throughout this specification should be taken to mean a C_1-C_6 alcohol which is not toxic for human use in a pharmaceutical context.

In one preferred embodiment of the invention the liquid pharmaceutical compositions are stable for at least 30 days at refrigeration temperatures and higher.

In a further preferred embodiment of the invention, the liquid pharmaceutical compositions of the invention comprise ifosfamide, solvent and optionally, conventional pharmaceutical carriers and excipients, wherein said solvent comprises 35 – 70% lower alcohol (based on the total weight of the solvent) and 30 – 65% polyol (based on the total weight of the solvent).

In a further preferred embodiment of the invention there is provided a liquid pharmaceutical composition comprising ifosfamide, solvent and optionally, conventional pharmaceutical carriers and excipients, wherein said solvent

comprises 70% lower alcohol (based on the total weight of the solvent) and 30% polyol (based on the total weight of the solvent, and said ifosfamide in present in an amount of 40% w/w of the total composition.

In another preferred embodiment the composition may contain one or more additional active agents to facilitate delivery of a so-called cocktail of drugs; a strategy often used in treatment of tumours. For example, the active agent may comprise ifosfamide and another anti-cancer compound, or ifosfamide and an active ingredient such as an anti-emetic, a uroprotector or any other anti-neoplastic agent. The uroprotector mesna is preferred.

The ifosfamide is preferably used in crystalline form. However, it is also possible to use amorphous, semi-solid or oily forms of ifosfamide. The ifosfamide may be used in the form of a lyophilizate.

The concentration of the ifosfamide in the composition in accordance with the invention amounts in general to 0.1-80%(w/w), preferably 10-70%(w/w) and particularly to 20-60%(w/w). [w/w = weight/weight].

The lower alcohol according to the invention is preferably ethanol more preferably absolute ethanol.

The polyol according to the invention may be one or a mixture of polyols selected from the group comprising polyethylene glycol (PEG) of molecular weight 200-1000; glycofurol, butylene glycol, glycerol and propylene glycol. Preferably, the polyol is propylene glycol, glycerol or polyethylene glycol of molecular weight 200-600. In the case of higher molecular weight PEGs which are solid at room temperature, low molecular weight PEG, ethanol, water or propylene glycol may be added to render the combination liquid at room temperature.

In another preferred embodiment, the composition according to the invention is stable for at least 180 days. This embodiment provides a composition that is well suited to transport and storage with minimal risk of degradation. More preferably, the composition is one in which at least 95-100% ifosfamide is present after 180 days storage at 40°C or less.

Desirably, the composition is substantially anhydrous, i.e. less than 15% water, and preferably less than 10% water, although the presence of water per se is not prohibited. It should be recalled however that since the oxazaphosphorins are

susceptible to hydrolysis, degradation may be minimised by limiting the presence of water. For example, when the polyol used is PEG 400, up to 10% water might be present without substantial negative effect.

The composition according to the invention may also include substances for the purposes of preservation (when the composition is diluted), isotonicity adjustment, stabilisation (such as antioxidants), pH adjusters (buffers) (for when the composition is diluted), chelating agents and other suitable excipients.

The compositions in accordance with the invention may, for adjusting and stabilizing the pH value of the diluted solutions, contain physiologically acceptable salts, physiologically acceptable alkalization mediums and/or physiologically acceptable acidization mediums. Inorganic and/or organic acids and/or inorganic salts and/or organic salts and inorganic bases and/or organic bases can be used. The acid, neutral and alkaline salts and their hydrates can also be used.

Examples of inorganic acids (mineral acids) may be but are not limited to hydrochloric, acid, carbonic acid, and phosphoric acid. Examples of inorganic bases may be but are not limited to ammonium hydroxide, alkali hydroxide like sodium hydroxide.

Examples of organic acids may be but are not limited to lactic acid, acetic acid, succinic acid, tartaric acid, ascorbic acid, malic acid, citric acid, fumaric acid, glutamic acid, benzoic acid, methane-sulphonic acid and ethanoic-sulphonic acid. Examples of organic bases may be, but are not limited to tromethamine (trometamol) and N-methylglucamine (meglumine) and the corresponding bases of succinic acid, tartaric acid, ascorbic acid, malic acid, citric acid, fumaric acid, glutamic acid, benzoic acid, methane-sulphonic acid and ethanoic-sulphonic acid in the form of their alkaline and alkaline earth salts.

In the solutions in accordance with the invention, salts of organic bases such as but not limited to mineral acid salts of tromethamine (trometamol) and N-methylglucamine (meglumine), preferably trometamol hydrochloride and meglumine hydrochloride may also be used.

As the preferred components for adjusting and stabilizing the pH value of the solution, phosphoric acid and salts of phosphoric acid and their hydrates may be used. Disodium hydrogen phosphate dihydrate and sodium dihydrogen phosphate

dihydrate are especially preferred. Additional preferred buffer components may be but are not limited to sodium lactate, sodium acetate, sodium acetate trihydrate and trisodium citrate trihydrate.

Especially preferred buffer components, alkalization mediums and acidization mediums may be but are not limited to salts of phosphoric acid and phosphoric acid, hydrochloric acid and sodium hydroxide.

For adjusting the isotonicity of the compositions, physiologically acceptable, ionic and/or non-ionic tonicisation mediums may be used. The physiologically acceptable tonicity adjustment mediums may be but are not limited to at least one carbohydrate that is selected from the group of 3-9C polyhydroxy alcohols.

In addition, this may involve one carbohydrate selected from the group of 5-10C monosaccharides, for example the pentitols, pentoses, hexitols and hexoses; this preferably involves dextrose, sorbitol or mannitol, with sorbitol and mannitol being especially preferred. It may involve at least one carbohydrate selected from the group of disaccharides, for example maltose, sucrose, lactose, maltobiose and maltotriose. Preferably it involves maltose, sucrose or lactose. The physiologically acceptable tonicity adjustment medium may also at least be one carbohydrate selected from the group of polysaccharides such as, for example, starch and dextran.

Further carbohydrates that are suitable as physiologically acceptable tonicity adjustment mediums may be selected from the group of cyclodextrins, for example from the alpha, beta and gamma cyclodextrins and their ethoxylated derivatives. Preferred are alpha, beta and gamma-cyclodextrins with alpha-cyclodextrins being especially preferred.

Suitable components for adjusting the tonicity therefore comprise, for example, glycerin (glycerol), threitol, trehalose, erythritol, pentaerythritol, erythrose, arabitol, arabinose, adonitol, xylitol, xylulose, sorbitol, sorbose, mannitol, mannose, dulcite, dextrose (glucose), fructose, maltose, sucrose, lactose, maltobiose, maltotriose, starch, hydroxyethyl starch (dextran), alpha, beta and gamma cyclodextrins and their alkoxyethylated derivatives, preferably threitol, erythritol, arabitol, adonitol, xylitol, sorbitol, mannitol, dulcite, dextrose (glucose), fructose, maltose, sucrose and lactose and particularly sorbitol, mannitol, dextrose (glucose),

fructose, maltose, sucrose and lactose and particularly sorbitol, mannitol, dextrose (glucose), fructose and lactose, with hexitols like sorbitol and/or mannitol being especially preferred.

The most preferred tonicity adjustment mediums that are physiologically acceptable are hexitols such as mannitol and/or sorbitol as well as sodium chloride.

Suitable preservatives for compositions of the invention may include but are not limited to methyl paraben, propyl paraben, phenol, benzylalcohol and sodium benzoate.

Suitable chelating agents for compositions of the invention may include but are not limited to disodium EDTA and sodium EDTA.

Suitable antioxidants for compositions of the invention may include but are not limited to ascorbic acid, sodium bisulfite, sodium metabisulfite, butylated hydroxy anisole (BHA), butylated hydroxy toluene (BHT), sodium formaldehyde sulphoxylate and monothioglycerol.

A preferred liquid pharmaceutical composition according to the invention is one comprising ifosfamide, ethanol and a polyol solvent selected from the group consisting of one or more of propylene glycol, glycerol or a polyethylene glycol having a molecular weight of 200-400 in adjunct with pharmaceutically acceptable carriers and excipients.

The compositions according to the invention may be prepared by simple admixture of the ethanol, polyol and ifosfamide whereupon stirring is applied to dissolve the active agent.

To prepare the compositions of the invention for parenteral infusion, suitable diluents include but are not limited to water, Ringer's solution, saline, dextrose and other similar infusion liquids.

Thus in another aspect of the invention there is provided a method of preparation of a parenteral infusion solution used in the treatment of tumours comprising admixing in a pharmacologically acceptable ratio a liquid pharmaceutical composition comprising ifosfamide, solvent and optionally, conventional pharmaceutical carriers and excipients wherein said solvent comprises 35-75% lower alcohol (based on the total weight of the solvent) and 25-65% polyol / based on the total weight of the solvent) and a diluent such as water, Ringer's solution,

saline, dextrose or other similar infusion liquids. Also provided is a parenteral infusion solution comprising a liquid pharmaceutical composition as described hereinabove which has been diluted to an acceptable concentration for infusion using a pharmaceutically acceptable diluent such as water, Ringer's solution, saline, dextrose or other similar infusion liquids

In a further aspect of the invention there is provided a use of a liquid pharmaceutical composition comprising ifosfamide, solvent and optionally, conventional pharmaceutical carriers and excipients wherein said solvent comprises 35-75% lower alcohol (based on the total weight of the solvent) and 25-65% polyol / based on the total weight of the solvent) for the preparation of a parenteral infusion solution for the treatment of tumours. Also provided is a method of treatment of tumours comprising administering to a patient requiring such treatment an effective amount of a parenteral infusion solution comprising a liquid pharmaceutical composition as hereinbefore described.

PREFERRED EMBODIMENTS

The following trials were conducted to test the stability of compositions according to the invention.

Example 1:

A solvent containing 35% w/w ethanol and 65% w/w PEG 400 was prepared. Ifosfamide was added to give an initial concentration of 10.27 mg/g of ifosfamide. After one month in storage at 4°C and correcting for weight loss due to the ethanol volatility, 100% of ifosfamide remained. After one month in storage at 50°C, 94.7% w/w of ifosfamide remained.

Example 2:

A solvent containing 75% w/w ethanol and 25% w/w PEG 400 was prepared. Ifosfamide was added to give an initial concentration of 11.42 mg/g of ifosfamide. After one month in storage at 4°C, 100% of ifosfamide remained. After one month in storage at 50°C, 97.9% w/w of ifosfamide remained.

Example 3:

A solvent containing 75% w/w ethanol and 25% w/w glycerol was prepared. Ifosfamide was added to give an initial concentration of 11.28mg/g of ifosfamide.

After one month in storage at 4°C, 100% w/w of ifosfamide remained. After one month in storage at 50°C, 97.0% w/w of ifosfamide remained.

Example 4:

A solvent containing 35% w/w ethanol and 65% w/w propylene glycol was prepared. Ifosfamide was added to give an initial concentration of 11.23 mg/g of ifosfamide.

After one month in storage at 4°C, 99.4% w/w of ifosfamide remained. After one month in storage at 50°C, 96.3% w/w of ifosfamide remained.

Example 5:

A solvent containing 75% w/w ethanol and 25% w/w propylene glycol was prepared. Ifosfamide was added to give an initial concentration of 12.23 mg/g of ifosfamide.

After one month in storage at 4°C, 99.3% w/w of ifosfamide remained. After one month in storage at 50°C, 98.0% w/w of ifosfamide remained.

Stability Trial Data is shown in the graphical representations marked figures 1-3 showing the advantages of the compositions according to the present invention as represented by examples 1 – 5 (fig.1), as against single solvent systems and the attempts of the prior art (fig.2 & 3). In each of the figures, the first bar refers to the amount of ifosfamide remaining at 4°C and the second bar refers to the amount of ifosfamide remaining at 50°C.

The following examples demonstrate production of liquid pharmaceutical compositions according to the invention.

Example 6:

40g of ifosfamide is transferred to a 200 ml glass conical flask. To this is added 60g of propylene glycol/absolute ethanol blend prepared previously in a 40:60 weight ratio. The flask is capped and the ifosfamide is dissolved by gentle agitation. A clear solution results containing ifosfamide 40 % w/w. The solution is filtered through 0.22 µm hydrophobic membrane filter in glass vials and sealed.

Example 7:

40g of ifosfamide is transferred to a 200 ml glass conical flask. To this is added 60g of glycerol/absolute ethanol blend prepared previously in a 40:60 weight ratio. The flask is capped and the ifosfamide is dissolved by gentle agitation. A

clear solution results containing ifosfamide 40 % w/w. The solution is filtered through 0.22 µm hydrophobic membrane filter in glass vials and sealed.

Example 8:

40g of ifosfamide is transferred to a 200 ml glass conical flask. To this is added 60g of PEG 400/absolute ethanol blend prepared previously in a 40:60 weight ratio. The flask is capped and the ifosfamide is dissolved by gentle agitation. A clear solution results containing ifosfamide 40 % w/w. The solution is filtered through 0.22 µm hydrophobic membrane filter in glass vials and sealed.

Example 9:

5 g of ifosfamide 40% w/w solution in propylene glycol/ethanol (40:60 w/w) was added to a standard 500ml PVC infusion bag containing 0.9% NaCl solution to provide a final concentration of ifosfamide in the bag of approximately 4mg/ml. 10ml of 100mg/ml mesna injection was added to this ifosfamide solution to provide a final mesna concentration in the same bag of approximately 2mg/ml. The solution was analysed for ifosfamide potency change after 24 hours. Potency loss of ifosfamide did not exceed 1.6% over 24 hours. No evidence of physical incompatibility was observed.

Comparative Examples

1. Discolouration studies and influence of additives:

Although slight discolouration is acceptable in an injectable product over time, significant discolouration is unacceptable and although not necessarily directly related, is usually associated with deterioration of the product.

The Asta patent teaches that certain physiologically acceptable polyols cannot be used as solvents for oxazaphosphorin compounds because their use leads to the development of unacceptable discolouration of said solutions (refer column 3 lines 20-25 of US 4,952,575). The polyols listed as unacceptable by Asta include propylene glycol, PEG 400 and others (glycerol is not listed). Asta claim solutions of oxazaphosphorins must contain greater than 80% v/v ethanol (and no other cosolvents) to render it acceptable with respect to chemical and colour stability. The balance is assumed for the purposes of the following example to

comprise water. Binary solvent systems of polyol and ethanol are not taught.

The Lyphomed patent teaches cyclophosphamide systems based on polyols which may contain up to 50% water and 30% ethanol. It is not reported that these solutions develop colour over time. Experiments however show that colour develops in Lyphomed formulations. Those that do contain water develop colour more slowly, but discolouration is not inhibited. The following formulations (for maximum chemical stability as taught by Lyphomed) were prepared containing 25% w/w cyclophosphamide and subjected to heat stress to demonstrate the level of degradation of the system:

Lyphomed System:	60°C
PEG 400 20% w/w in PG (Lyphomed most preferred)	orange colour develops (3-6 hours)
PEG 400 20%, ethanol 10% w/w in PG (Lyphomed)	orange colour develops (6 hours+)
PEG 400 20% ethanol 30% w/w in PG (Lyphomed)	orange colour develops (6 hours+)

The following examples show the discolouration occurring in compositions according to the invention and according to the prior art in relation to 10% w/w ifosfamide solutions in the following solvent blends:

Comparative solvent system	Colour Development
PG 100%	Yellow colour (40°C/1 month)
Glycerol 100%	Orange colour (40°C/1 month)
PEG 400 100%	Yellow/Orange colour (40°C/1 month)
>80% ethanol (Asta)	Solutions colourless
PG 25-65% w/w in EtOH(invention)	Solutions remain essentially colourless (40°C/6months) ranging from colourless to pale straw colour

Glycerol 25-65% w/w in EtOH (invention)	Pale straw colour
Glycerol 25-65% w/w in ethanol + sodium metabisulphite (satn.) or sodium formaldehyde sulphoxylate (satn.) or monothioglycerol (0-5%) (invention)	Colourless to very pale straw colour

2. Stability trials

Stability data from compositions according to the invention, in contrast to teachings in US 4,952,575 – Asta, show that anhydrous ethanolic solutions of ifosfamide containing less than 80% v/v ethanol and containing a second non-aqueous cosolvent (best results with propylene glycol) are chemically stable and undergo minimal discolouration. US 4,952,575 teaches that ifosfamide is only stable in ethanolic solutions containing 80-100 % ethanol and that trials carried out on solutions of oxazaphosphorins in other cosolvents (propylene glycol, PEG 400, glycerol and other pharmaceutical glycols) lead to significant discolouration (refer column 3 line 20 of US 4,952, 575).

SUMMARY TABLE OF INDICATIVE STABILITY DATA FOR IFOSFAMIDE 10% W/W AND 40% W/W SOLUTIONS

Solvent System containing Ifosfamide 10% w/w	Potency of Ifosfamide as % of Expected Concentration (as analysed)				Potency Loss (by formation of degradants)		Appearance of Solution	
5°C	*T=0*	*T=1*	*T=3*	*T=6*	*T=3*	*T=6*	*T=3*	*T=6*
Glycerol/EtOH (25/75)	100.7	Na	100.6	99.0	–0.20%	–0.18%	Clear, colourless solution	Clear, colourless solution
Glycerol/EtOH (25/75) + NaMBS	99.8	Na	99.8	98.9	–0.20%	–0.14%	Clear, colourless solution	Clear, colourless solution
Propylene Glycol/Eth (25/75)	100.7	Na	99.7	98.7	–0.26%	–0.22%	Clear, colourless solution	Clear, colourless solution
Propylene Glycol/EtOH (65/35)	99.6	Na	99.8	98.1	–0.28%	–0.24%	Clear, colourless solution	Clear, colourless solution
PEG 400/EtOH (25/75)	100.0	Na	100.4	Na	0.50%	Na	Clear, colourless solution	Clear, colourless solution
PEG 400/EtOH (65/35)	100.0	Na	97.7	Na	0.50%	Na	Clear, colourless solution	Clear, colourless solution
0.9% Sodium Chloride Soln.	99.5	Na	Na	Na	Na	Na	Clear, colourless solution	Clear, colourless solution
Water	99.5	Na	Na	Na	Na	Na	Clear, colourless solution	Clear, colourless solution
40°C	*T=0*	*T=1*	*T=3*	*T=6*	*T=3*	*T=6*	*T=3*	*T=6*
Glycerol/EtOH (25/75)	100.7	100.6	97.4	95.9	2.90%	4.96%	Clear, slight straw coloured soln.	Clear, pale straw-coloured solution
Glycerol/EtOH (25/75) + NaMBS	99.8	100.2	98.7	95.6	2.60%	4.72%	Clear, slightly straw coloured soln.	Clear, very pale straw-coloured solution
Propylene Glycol/Eth (25/75)	100.7	100.7	98.9	98.3	1.82%	4.22%	Clear, colourless solution	Clear, colourless solution
Propylene Glycol/EtOH (65/35)	99.6	99.6	97.7	94.1	2.98%	6.40%	Clear, slight straw coloured soln.	Clear, very pale straw-coloured solution
PEG 400/EtOH (25/75)	100.0	100.2	96.8	Na	3.30%	Na	Clear, slight straw coloured soln.	Clear, straw-coloured solution
PEG 400/EtOH (65/35)	100.0	99.7	96.3	Na	5.20%	Na	Clear, yellow coloured soln.	Clear, yellow solution
0.9% Sodium Chloride Soln.	99.5	64.19	Na	Na	Na	Na	Clear, colourless solution	Clear, colourless solution
Water	99.5	60.98	Na	Na	Na	Na	Clear, colourless solution	Clear, colourless solution

Solvent System containing Ifosfamide 40% w/w	Potency of Ifosfamide as % of Expected Concentration (as analysed)				Potency Loss (by formation of degradants)		Appearance of Solution	
5°C	*T=0*	*T=1*	*T=3*	*T=6*	*T=3*	*T=6*	*T=3*	*T=6*
Glycerol/EtOH (25/75)	101.5	Na	99.5	Na	Na	Na	Clear, colourless solution	Clear, colourless solution
Glycerol/EtOH (25/75) + NaMBS	105.2	Na	101.7	Na	Na	Na	Clear, colourless solution	Clear, colourless solution
Propylene Glycol/Eth (25/75)	105.8	Na	99.2	100.5	–0.40%	–0.14%	Clear, colourless solution	Clear, colourless solution
Propylene Glycol/EtOH (65/35)	99.7	Na	99.2	98.6	–0.50%	–0.18%	Clear, colourless solution	Clear, colourless solution
PEG 400/EtOH (25/75)	103.8	Na	Na	Na	Na	Na	Clear, colourless solution	Clear, colourless solution
PEG 400/EtOH (65/35)	105.6	Na	Na	Na	Na	Na	Clear, colourless solution	Clear, colourless solution
40°C	*T=0*	*T=1*	*T=3*	*T=6*	*T=3*	*T=6*	*T=3*	*T=6*
Glycerol/EtOH (25/75)	101.6	Na	97.6	Na	Na	Na	Clear orange/Yellow solution	Clear, pale yellow solution
Glycerol/EtOH (25/75) + NaMBS	105.2	Na	102.0	Na	Na	Na	Clear yellow solution	Clear, very pale yellow solution
Propylene Glycol/Eth (25/75)	105.8	Na	97.3	95.9	2.30%	3.92%	Clear, very pale straw solution	Clear, very pale straw-coloured soln.
Propylene Glycol/EtOH (65/35)	99.7	Na	97.8	94.9	3.30%	5.16%	Clear straw coloured solution	Clear, yellow solution
PEG 400/EtOH (25/75)	103.8	Na	Na	Na	Na	Na	Clear yellow solution	Clear, bright yellow solution
PEG 400/EtOH (65/35)	105.6	Na	Na	Na	Na	Na	Clear bright yellow solution	Clear, dark yellow solution

5 Na = Not analysed. Intensely discoloured solutions were deemed chemically unstable and were not analysed. NaMBS = Sodium Metabisulphite.

3. Solvent volatility and syringeability

A reduction in ethanol content through the introduction of other less volatile pharmaceutically acceptable non-aqueous cosolvents does result in a reduction in overall solvent volatility. This is demonstrated in figures 4 and 5.

3. Syringeability and extrudability data.

Tests were conducted to measure the syringeability of compositions according to the invention with the following outcomes:

Solvent (constant volume) contents)	Force (required to expel syringe
Water	3.4 N
Propylene Glycol	65.9 N
PEG 400	101.5 N
Glycerol	188.2 N
Absolute Ethanol	4.1 N
25% PEG400/75% Ethanol	5.6 N
25% Glycerol/75% Ethanol	6.7 N
25% Propylene Glycol/75% Ethanol	5.6 N
65% PEG400/35% Ethanol	17.4 N
65% Glycerol/35% Ethanol	50.6 N
65% Propylene Glycol/35% Ethanol	14.8 N

These data confirm that inclusion of viscous cosolvents in the proportions claimed improves the syringeability of the vehicle (compared to pure ethanolic solutions) by virtue of increased viscosity of the vehicle.

It will be appreciated that the compositions of the invention provide significant advantages in the transport, storage and handling of ifosfamide injectable compositions for use in treatment of tumours. It will be further appreciated that the scope of this invention need not be limited to the embodiments and examples herein, but extends to the general principal of stabilization of ifosfamide by polyol/ethanol solvent mixtures.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A liquid pharmaceutical composition for parenteral administration comprising ifsofamide, solvent and optionally, conventional pharmaceutical carriers and excipients, wherein said solvent comprises 35–75% lower alcohol (based on the total weight of the solvent) and 25–65% polyol (based on the total weight of the solvent).

2. A liquid pharmaceutical composition as claimed in claim 1, which is stable at refrigeration temperatures and higher for at least 30 days.

3. A liquid pharmaceutical composition as claimed in claim 1 which is stable at refrigeration temperatures and higher for at least 180 days.

4. A liquid pharmaceutical composition as claimed in any one of claims 1 – 3 wherein said polyol solvent is one or more solvents selected from the group consisting of polyethylene glycols (PEG) of molecular weight 200-1000, glycofurol, butylene glycol, glycerol and propylene glycol.

5. A liquid pharmaceutical composition as claimed in any one of claims 1 – 4 wherein said polyol solvent is one or more solvents selected from the group consisting of propylene glycol, glycerol and polyethylene glycol of molecular weight 200-600.

6. A liquid pharmaceutical composition as claimed in any one of claims 1 – 3 wherein said lower alcohol solvent is ethanol.

7. A liquid pharmaceutical composition as claimed in any one of claims 1 – 6 wherein the lower alcohol solvent is absolute ethanol.

8. A liquid pharmaceutical composition as claimed in any one of claims 1 – 7 additionally comprising a second active agent selected from the group consisting of anti-emetics and uroprotectors, and other anti-neoplastic agent.

9. A liquid pharmaceutical composition as claimed in any one of claims 1 – 8 comprising up to 15% w/w water.

10. A liquid pharmaceutical composition as claimed in any one of claims 1 – 8 which is substantially anhydrous.

11. Use of a liquid pharmaceutical composition comprising ifosfamide, solvent and optionally, conventional pharmaceutical carriers and excipients wherein said solvent comprises 35-75% lower alcohol (based on the total weight of the solvent) and 25-65% polyol / based on the total weight of the solvent) for the preparation of a parenteral infusion solution for the treatment of tumours.

12. A parenteral infusion solution comprising a liquid pharmaceutical composition as claimed in any one of claims 1 – 10 which has been diluted to an acceptable concentration for infusion using a pharmaceutically acceptable diluent.

13. Method of treatment of tumours comprising administering to a patient requiring such treatment an effective amount of a parenteral infusion solution as claimed in claim 12.

14. Use of a parenteral infusion solution as claimed in claim 12 for the treatment of tumours.

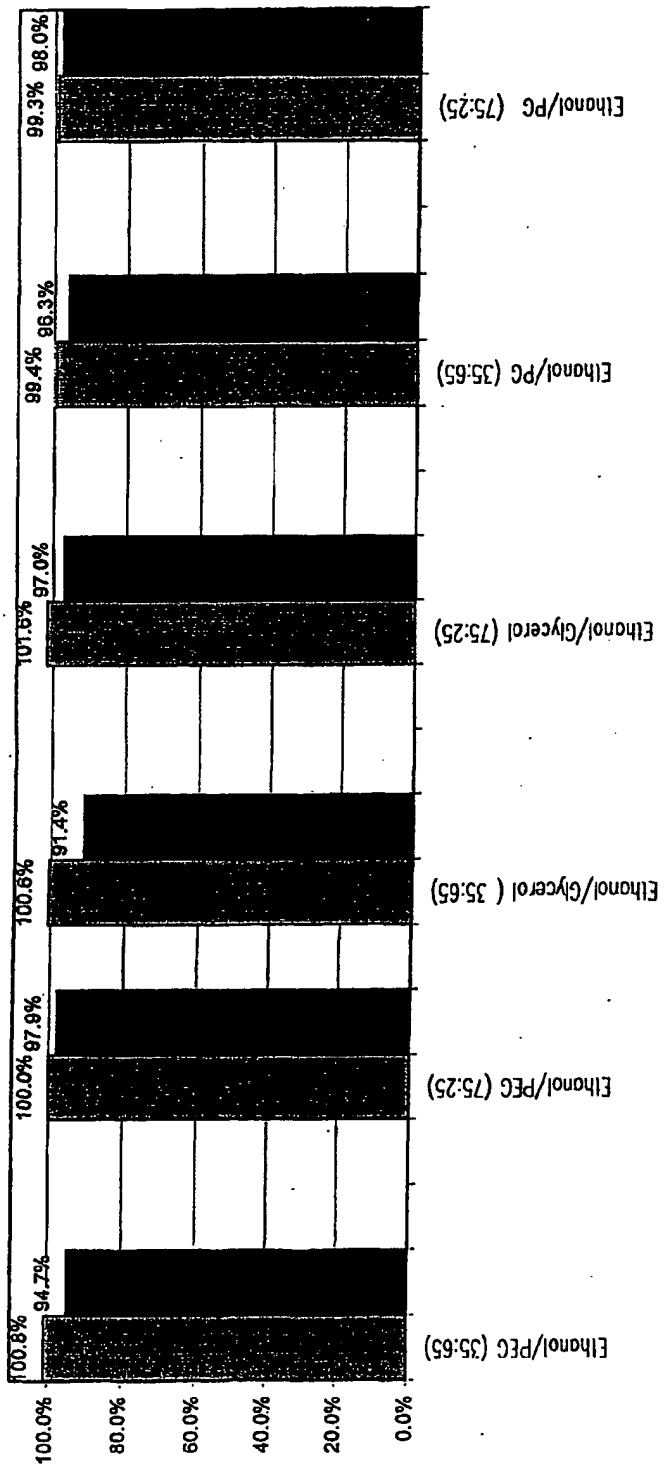


Figure 1. Ethanol Containing Anhydrous Systems
Ifosfamide Remaining after One Month Storage at 4°C and 50°C
(weight loss corrected)

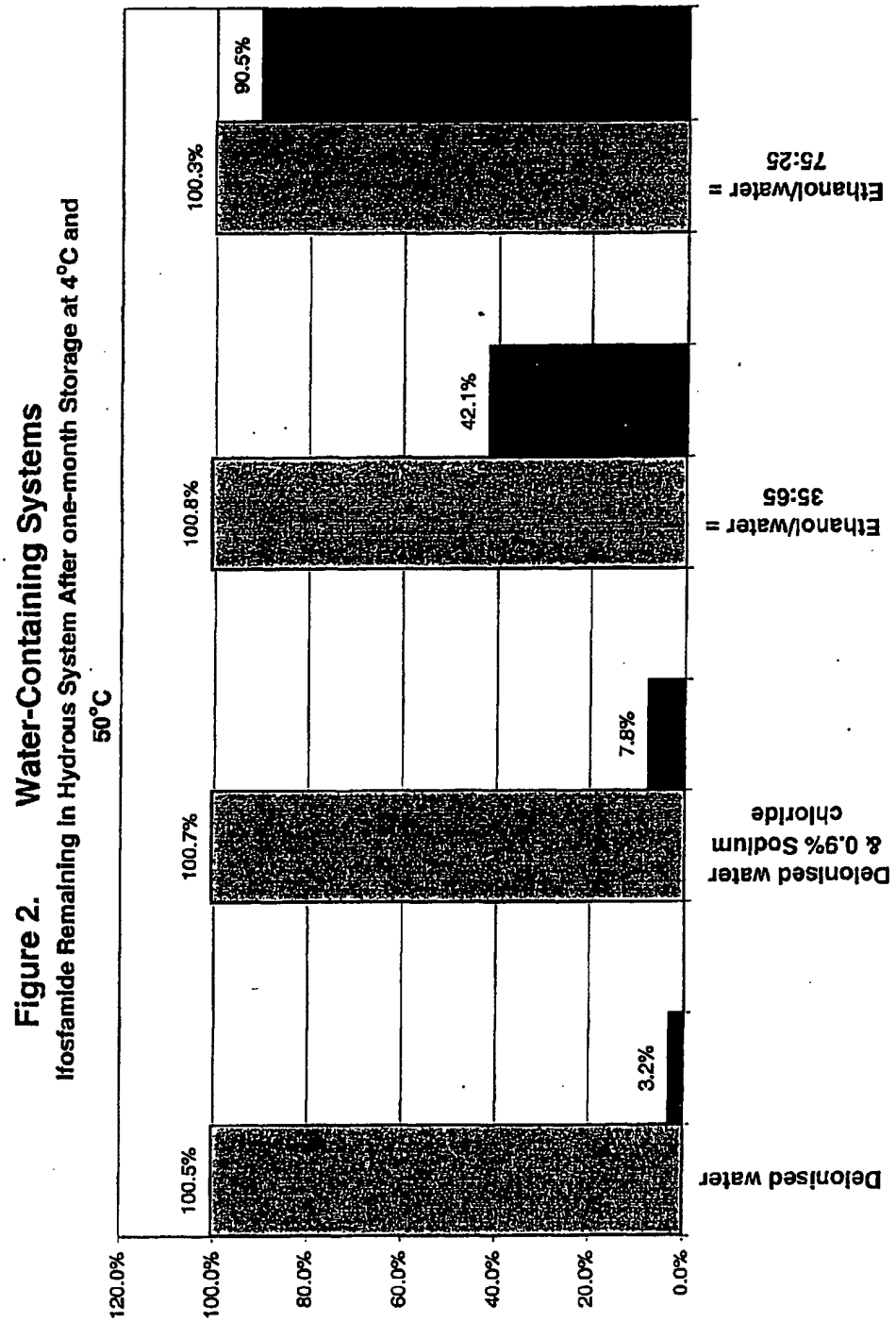


Figure 2. Water-Containing Systems
Ifosfamide Remaining in Hydrous System After one-month Storage at 4°C and 50°C
120.0%
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
100.5%
3.2%
100.7%
7.8%
100.8%
42.1%
100.3%
90.5%
Deionised water
Deionised water & 0.9% Sodium chloride
Ethanol/water = 35:65
Ethanol/water = 75:25

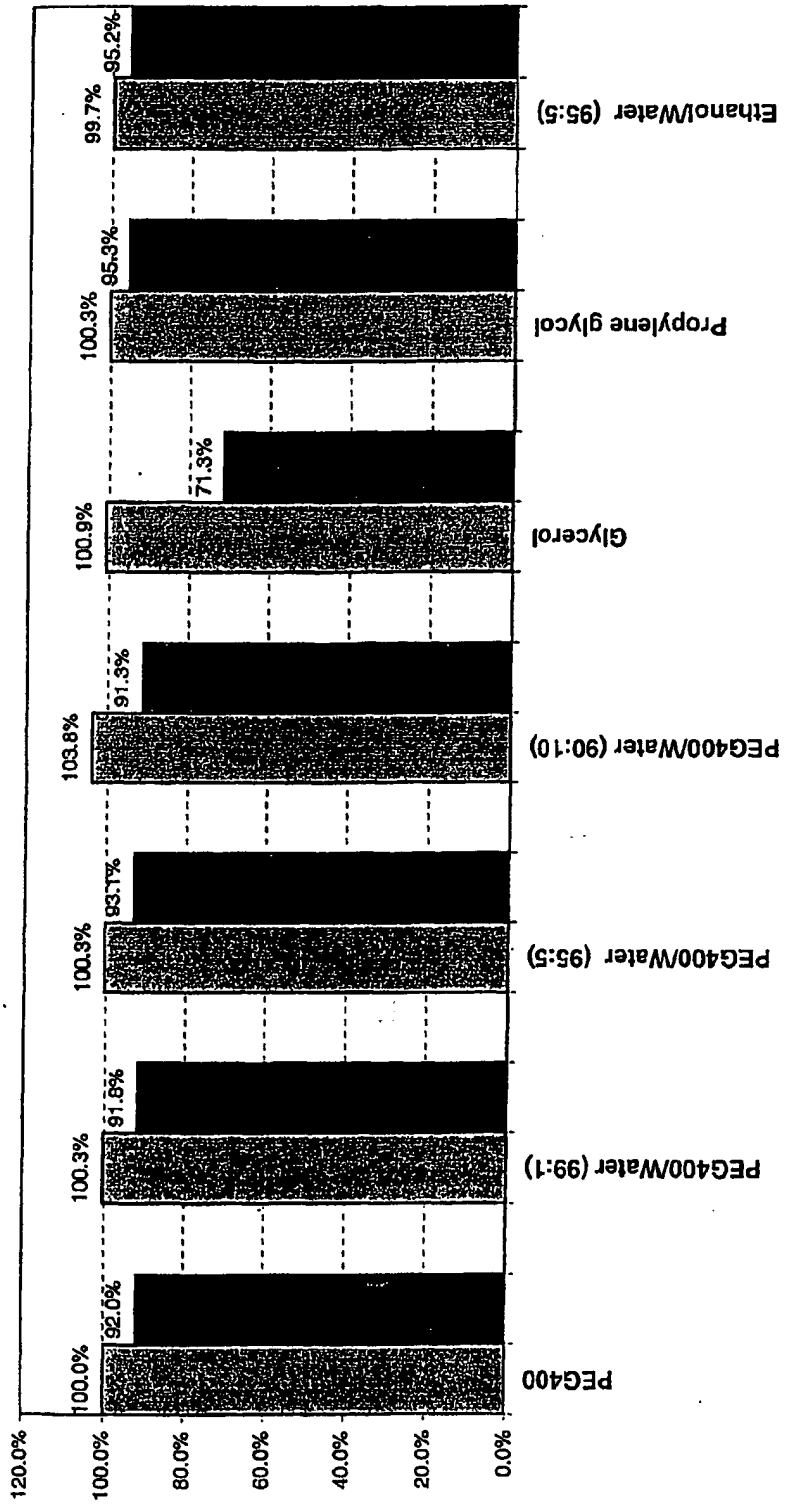


Figure 3. Solvent Systems With Water as Minor Component
Ifosfamide Remaining after one-month Storage at 4°C and 50°C

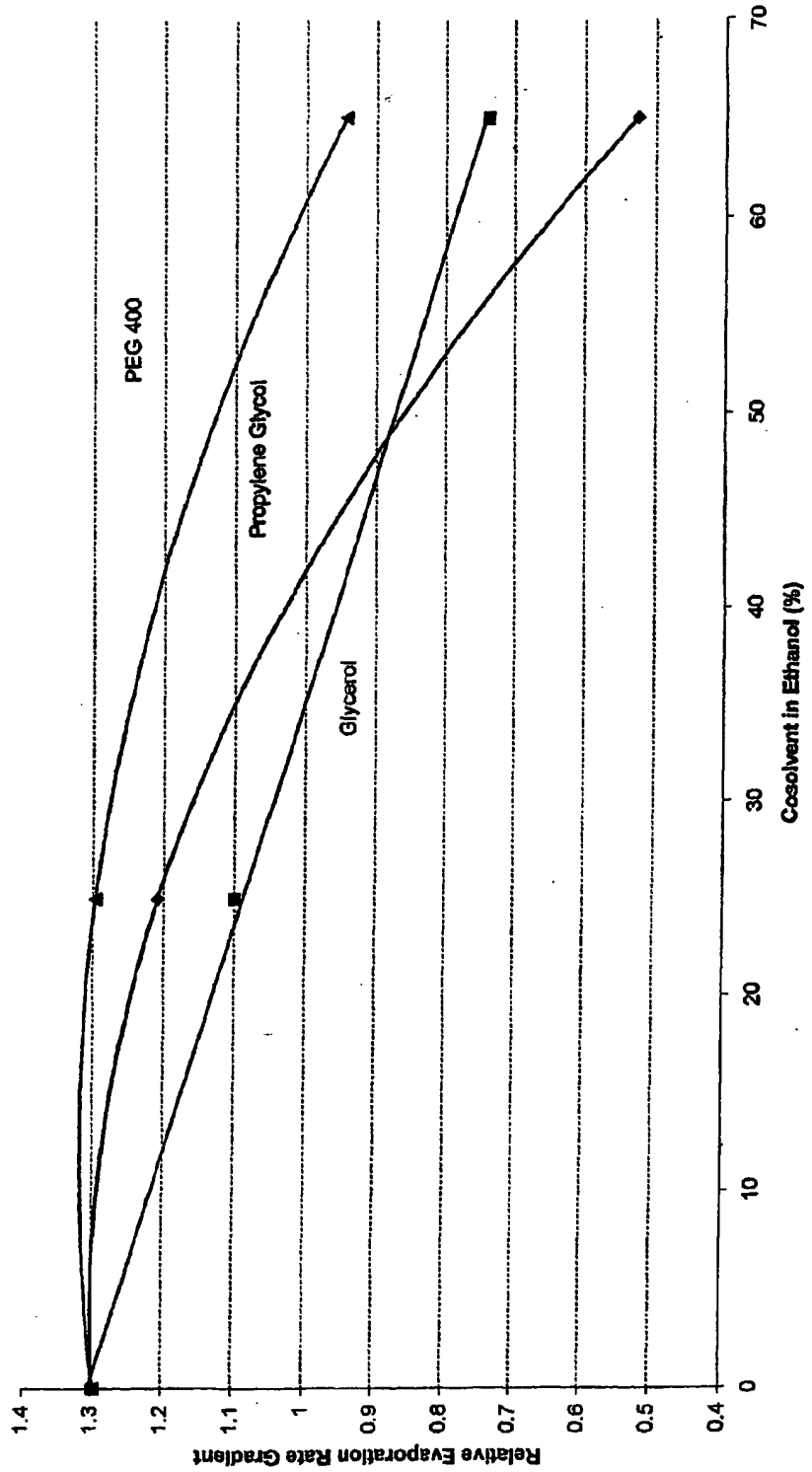
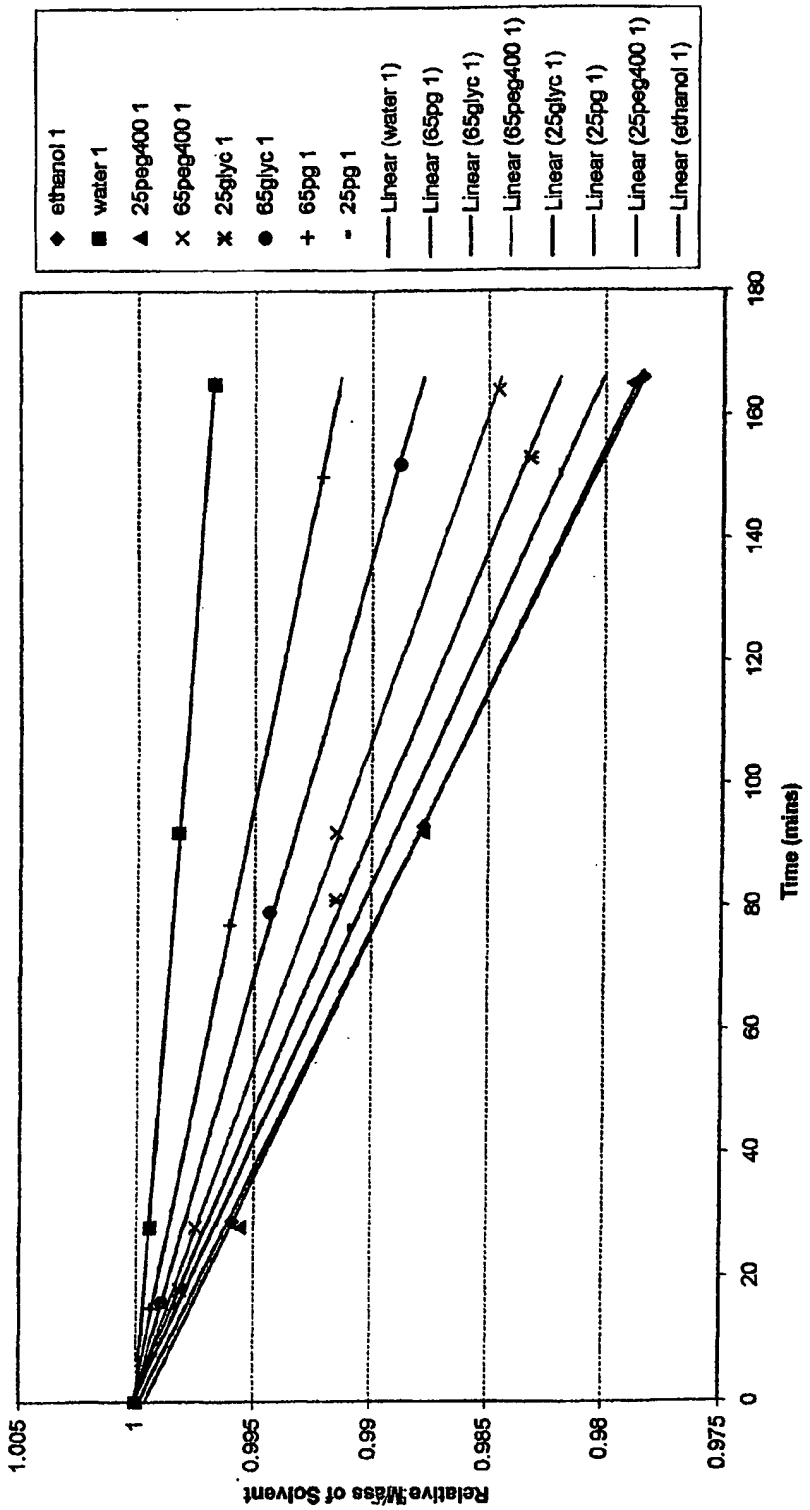


Figure 4. RELATIVE EVAPORATION RATE VERSUS THE PERCENTAGE OF COSOLVENT IN ETHANOL

Figure 5. RELATIVE LOSS OF SOLVENT THROUGH EVAPORATION OVER TIME



INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 01/00789

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[7]: A61K 31/675; A61P 35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
FILE WPAT AND CHEM ABS. SEE KEYWORDS BELOW

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DERWENT WPAT AND CHEMICAL ABSTRACTS DATABASE, KEYWORDS: IFOSFAMIDE, OXAZAPHOSPHORINS, HOLOXAN, ?GLYCOL, GLYCEROL, PEG, POLYOL, ETHANOL AND PROPANOL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/18973 A(STADA ARZNEIMITTEL AG) 22 April 1999 See whole document	1-14
Y	US 4,952,575 A (SAUERBIER D ET AL) 28 August 1990 See whole document	1-14
Y	US 4,879,286 A (ALAM S. ABU ET AL) 7 November 1989 See whole document	1-14

☐ Further documents are listed in the continuation of Box C

☒ See patent family annex

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 August 2001	6 SEPTEMBER 2001
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No.: (02) 6285 3929	Authorized officer **ARATI SARDANA** Telephone No.: (02) 6283 2627

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU 01/00789

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	9918973	AU	15550/99	EP	1023075		
US	4952575	AU	75549/87	CA	1289886	DK	3593/87
		EP	254902	FI	873064	IL	83141
		JP	63023888	PT	85293	ZA	8705059
		DE	3722043				
US	4879286	NONE					

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